



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification<sup>4</sup> :</b> <b>A61L 27/00</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 86/ 00533</b> <b>(43) International Publication Date:</b> 30 January 1986 (30.01.86)
<b>(21) International Application Number:</b> PCT/NL85/00027 <b>(22) International Filing Date:</b> 10 July 1985 (10.07.85) <b>(31) Priority Application Number:</b> 8402178 <b>(32) Priority Date:</b> 10 July 1984 (10.07.84) <b>(33) Priority Country:</b> NL  <b>(71) Applicant (for all designated States except US):</b> RIJK-SUNIVERSITEIT TE GRONINGEN [NL/NL]; Broerstraat 5, NL-9712 PC Groningen (NL).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> LEENSLAG, Jan, Willem [NL/NL]; De Einthovenlaan 29, NL-7002 HE Doetinchem (NL). PENNING, Albert, Johan [NL/NL]; Ettenlaan 3, NL-9331 BE Norg (NL). VETH, René, Pieter, Hendrick [NL/NL]; De Wilgen 2-4, NL-9781 ME Bedum (NL). JANSEN, Henricus, Wilhelm, Bernhard [NL/NL]; Verweylaan 14, NL-9752 GM Haren (NL).		<b>(74) Agent:</b> URBANUS, H., M.; Vereenigde Octrooibureaux, Nieuwe Parklaan 107, NL-2587 BP The Hague (NL).  <b>(81) Designated States:</b> AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> BONE IMPLANT  <b>(57) Abstract</b>  An implant article for treatment in reconstructive surgery of damage caused to bony material, said article comprising a composite of fibre material which may or may not be bio-degradable and is incorporated in a porous matrix of a bio-degradable organic polymer material.		

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Title: Bone implant.

The present invention relates to an implant article for treatment in reconstructive surgery of damage caused to bony material.

At present it is being recognised that the meniscus is an  
5 important component of the knee-joint in case of injuries the repair or preservation of the undamaged part of which is preferred over the surgical removal of the meniscus. In this connection experience has shown that a damaged, e.g. torn, meniscus can only be healed if vascularisation of the injury is possible. It has further been  
10 established with animals by way of experiment that by reconstructive surgery of wedge-shaped and longitudinal injuries of the meniscus healing is effected by means of a synovial flap and after implantation of an implant article consisting of carbon fibres (Clin. Orthop. 181 (1983) 250-254). Although implantation of carbon fibres has proved  
15 to be a promising method of treating damaged menisci, technical deficiencies have become apparent, in most cases relating to a tendency to dislocation of the bundle of carbon fibres.

It is an object of the present invention to provide an implant article giving a solution for the above-mentioned drawback and  
20 permitting a more rapid ingrowth of tissue and vessels.

According to the present invention there is provided for this purpose an implant article of the above-mentioned type which is characterised by a composite of fibre material which may or may not be bio-degradable and is incorporated in a porous matrix of a bio-  
25 degradable organic polymer material.

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The bio-degradable organic polymer material used for the matrix may be a polyurethane material, e.g., a polyether urethane, a polyester urethane and a polyether urea urethane; a polylactide material, e.g., a poly(L-lactide), a poly(D-lactide) and a poly(D,L-lactide); a poly-glycolide material, e.g., a polyglycolic acid and copolymers composed of the different lactide materials, glycolide materials and other hydroxycarboxylic acids, as well as homopolymers and copolymers of amino acids. The individual polymer materials of mixtures thereof may be used, if required, with other bio-degradable polymer materials, e.g., with a porous polyamide material.

The fibre material for reinforcing the composite according to the invention may be incorporated in the matrix as loose fibres, however, also as a woven fabric, a knitted fabric or another coherent combination of fibres. The fibres to be used according to the invention may or may not be bio-degradable and comprise, e.g., carbon fibres; sufficiently strong polyethylene fibres; poly(L-lactide fibres), if required, with additives, e.g., low-molecular additives or bio-degradable homopolymers and/or copolymers; polyglycolide fibres; polyamide fibres, e.g., poly(p-aminobenzoic acid) fibres; polyamide fibres, e.g., nylon fibres, or fibres of glycolide lactide copolymers.

The composite according to the invention may also include, e.g., materials capable of accelerating the bio-degradability of the matrix and the bio-degradability of the fibres, promoting ingrowth of tissue, having antibacterial activity and/or analgetic activity.

Examples of such materials are citric acid, sodium citrate, salicylic acid, aspirin, tartaric acid, magnesium chloride and calcium phosphate.

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It has turned out that the composite according to the invention is a product which, in addition to bio-degradable and bio-compatible properties, is also microporous and is therefore eminently suitable for effecting vascularisation or ingrowth of tissue, without which properties the repair of torn bone material, such as cartilage material of the meniscus, must be ruled out. By embedding the reinforcing fibre material according to the invention in a matrix of a bio-degradable organic polymer material, no shift of the fibres appears to occur during the healing process.

10 Although the properties of the composite according to the invention have been elucidated above, especially by means of the reconstructive-surgical treatment of meniscus injuries, the use of the composite is not restricted thereto.

A composite according to the invention useful in practice for the repair of large wedge-shaped tears of the meniscus in dogs has appeared to be an implant article made of a polyurethane-poly(L-lactide) organic polymer material as the matrix, in combination with carbon fibres. The composite formed therefrom was bio-degradable and bio-compatible and further microporous.

20 The invention is illustrated by the following example.

Example

A. The materials used in this example for the preparation of the composite.

There was used a segmented poly(ether urethane) commercially available under the trade name Estane 5714F1 (Goodrich, Co., Breckville, Ohio, U.S.A.)

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The polylactide used was poly(L-lactide) ( $\bar{M}_v = 3.5 \times 10^5$ ), synthesised according to a process disclosed in the literature (Polymer 23 (1982) 1587).

To reinforcing material used was commercially available carbon  
5 fibres (Grafil EAS), (Courtaulds, Ltd., Coventry, England).

Sodium citrate (Merck) was further added to the subsequently prepared polymer solutions, in a low concentration.

B. The preparation of the polymer solutions and the carbon fibres.

The polyurethane was reprecipitated 5 times (3 times from  
10 N,N-dimethylformamide (DMF), then 1 time from tetrahydrofuran (THF) and finally, 1 more time from DMF). The precipitant used was demineralised water. Reprecipitation was carried out at room temperature. The precipitated polyurethane was washed with ethanol (96%), and air dried for 1 night, then dried in a vacuum stove for 1 more hour at  
15  $T = 50^\circ\text{C}$ .

Separate poly(L-lactide)- and polyurethane solutions were prepared which were added to each other just before each use.

The solvent used for both polymers was a mixture of DMF and THF (DMF:THF = 75:25%  $\frac{V}{V}$ ). The poly(L-lactide) solution was saturated  
20 with sodium citrate.

The total polymer concentration of the final solution was 4%  $\frac{W}{V}$ ; both polymers were mixed in a ratio of polyurethane:poly(L-lactide)=80:20%  $\frac{W}{W}$ .

The composite involved in the in vivo examination was  
25 prepared from a 4%  $\frac{W}{V}$  solution. (For uses requiring larger pores this could be achieved by further diluting the polymer solutions.

A dilution of, e.g., 4%  $\frac{W}{V}$ , for instance, gave an average pore size of

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$\pm 100$   $\mu\text{m}$ , and a dilution of 3%  $^W/v$  gave an average pore size of  $\pm 250$   $\mu\text{m}$ ).

The carbon fibres were extracted with an acetone-THF mixture (acetone:THF = 50:50%  $^V/v$ ) for 24 hours at room temperature and then air dried. Subsequently, the fibres were cut to the desired length.

### C. Preparation of the porous polymer sheets.

#### 1. Without carbon fibres.

(a) A tube provided with a Teflon layer was kept in the final polymer solution for 4 seconds ( $T = 20^\circ\text{C}$ ),

(b) Then the tube was air dried for 15-20 seconds, with a rotary movement being performed.

(c) Subsequently the tube was immersed in a non-solvent (water,  $T = 45^\circ\text{C}$ ); residence time 2-3 minutes.

(d) Then the tube was placed in cold water ( $T = 10^\circ\text{C}$ , residence time 2 minutes) and subsequently in ethanol (96%), (residence time: 2 minutes); finally, the tube was immersed in water ( $T = 20^\circ\text{C}$ , residence time: 3 minutes).

(e) After that the outermost polymer layer was carefully dried with blotting-paper. Thus one porous polymer layer was obtained.

This operation was repeated until a porous polymer sheet was obtained having the desired thickness and without carbon fibres.

#### 2. With carbon fibres.

(a) For a method of preparing a porous polymer sheet with carbon fibres 10 layers of the polymer were applied to the tube in the manner as described above.

(b) Then the carbon fibres (2 layers, crosswise arranged over each other) were affixed to the tube and the immersing/coating process was continued with another 10 polymer layers.

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According to another method carbon fibres were disposed in a layer of polymer solution (2 layers, crosswise arranged over each other), after which the non-solvent (water,  $T = 45^{\circ}\text{C}$ ) was added with an atomizer. After the above-described treatment the whole was repeated  
5 for 4 more times. Then the carbon fibres were sufficiently fastened in the polymer matrix to continue the immersing/coating process with this fabric (see C. (a)-(e)), with the composition being effected on both sides.

The final composite was built up of layers of the porous sheets  
10 as obtained under C., the polymer sheets with and without carbon fibres being alternately processed in the final composite. The different layers were bonded together with a 1%  $\text{w/v}$  polymer solution, using the process mentioned under C. Thus the composite was brought to the required dimensions from which the final meniscus prosthesis could be cut to  
15 size.

It is noted that, in addition to the above-mentioned mixture DMF/THF 75:25%  $\text{v/v}$ , e.g., also DMF/1,4-dioxane mixtures (75-25%  $\text{v/v}$ ) (or other ratios) may be used. The resulting materials thereby obtain a somewhat different porous structure which may be very suited for ortho-  
20 pedic uses. Suitable solvents are further dimethylacetamide and dimethylsulfoxide.

In the above-indicated manner and with the indicated starting materials a composite was prepared on the basis of a mixture composed of 95 wt.% polyurethane and 5 wt.% poly(L-lactide), using the process  
25 described under C.2. (a). The resulting composite was microporous with a pore size of 35-50  $\mu\text{m}$ .



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With the composite a research into the chances of a torn meniscus to be healed was conducted with a group of 12 dogs. Of each of the dogs a meniscus was surgically provided with a large wedge-shaped incision extending over approximately 30% of the meniscus.

5 For the repair of the menisci the composite was folded double and sewed together, then adapted to the actual size of the damaged meniscus to be treated, placed in the incision and sewed together therein with 3-0 Dexon sewing-thread. The wound was closed and the dogs were given an opportunity to get on their legs again as soon as possible.

10 Four weeks after the operation the progress of the healing process was evaluated arthroscopically, morphologically and histologically in the manner appropriate therefor from a medical point of view.

It turned out that all the implant elements except one had remained in position, and that ingrowth of fibrous fibro-cartilaginous material  
15 had taken place over a substantial distance from the place where the implant element is in contact with the surrounding meniscus.

In two cases the meniscus proved to have healed already completely.

After a period of 14-19 weeks the implant element proved to have been completely absorbed in the meniscus.

20 In a combination of a wedge-shaped and a longitudinal tear in the meniscus of rabbits, application of the implant element to these injuries of the meniscus proved to induce nearly complete healing.

Summarizing, the composite according to the invention proves  
25 to be easy in handling owing to applying the organic polymer matrix and conducive to ingrowth of tissue and vessels because of the micro-

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porous condition thereof. These last-mentioned properties are necessary for enabling a damaged meniscus to heal, as appears from

S.S. Arnockzy et al., "The microvasculature of the meniscus and its response to surgery", Am.J. Sports med. 11 (1983) 131;

5 R.P.H. Veth et al., Clin. Orthop. 175 (1983) 259 and Clin.Orthop. 181 (1983) 212.

CLAIMS

1. An implant article for treatment in reconstructive surgery of damage caused to bony material, characterised by a composite of fibre material which may or may not be bio-degradable and is incorporated in a porous matrix of a bio-degradable organic polymer material.
- 5 2. An implant article according to claim 1, characterised in that the bio-degradable organic polymer material is a polyurethane, a polylactide, a polyglycolide, a polyamide, a polyester and/or a copoly ( $\alpha$ -amino acid) material.
3. An implant article according to claim 2, characterised in that  
10 the polyurethane material is a polyether urethane, a polyester urethane and/or a polyether urea urethane.
4. An implant article according to claim 2, characterised in that the polylactide material is a poly(L-lactide), a poly(D-lactide) and/or a poly(D,L-lactide).
- 15 5. An implant article according to claim 2, characterised in that the polyglycolide material is polyglycolic acid.
6. An implant article according to claim 2, characterised in that the polyamide material is a porous polyamide.
7. An implant article according to claim 1, characterised in  
20 that it contains the fibre material as loose fibres and/or as a coherent combination of fibres and that the employable fibre material is carbon fibres, polyethylene fibres, poly(L-lactide) fibres, polyglycolide fibres, polyaramide fibres, polyamide fibres and/or fibres of glycolide-lactide copolymers, as well as fibres of other poly( $\alpha$ -hydroxycarboxylic acids),

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a poly( $\beta$ -methylpropiolactone), poly(dioxanone), polyglycine and other poly( $\chi$ -amino acids), polypropylene and polyesters.

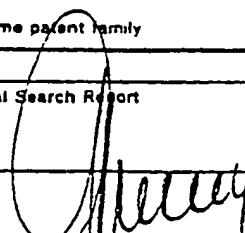
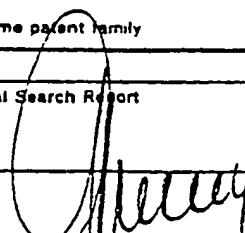
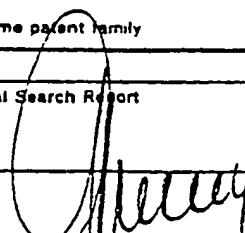
8. An implant article according to claim 7, characterised in that the poly(L-lactide) fibres contain low-molecular additives  
5 and/or bio-degradable homopolymers and/or copolymers.

9. An implant article according to claim 1, characterised in that the organic material is prepared from a mixture of a polyurethane, a poly(L-lactide) and a polyamide in different ratios.

10. An implant article according to claim 9, characterised in  
10 that the organic material is prepared from approximately 80-95% polyurethane and 20-5% poly(L-lactide).

# INTERNATIONAL SEARCH REPORT

International Application No PCT/NL 85/00027

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup> According to International Patent Classification (IPC) or to both National Classification and IPC IPC <sup>4</sup> : A 61 L 27/00																																
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; padding: 2px;">Minimum Documentation Searched <sup>7</sup></div> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%; border: none; padding: 2px;">Classification System  </td> <td style="border: none; padding: 2px;">Classification Symbols</td> </tr> <tr> <td style="border: none; padding: 2px;">IPQ<sup>4</sup>  </td> <td style="border: none; padding: 2px;">A 61 L</td> </tr> </table> <div style="text-align: center; padding: 2px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup></div>			Classification System	Classification Symbols	IPQ <sup>4</sup>	A 61 L																										
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<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%; padding: 2px;">Category <sup>9</sup></th> <th style="width: 70%; padding: 2px;">Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup></th> <th style="width: 20%; padding: 2px;">Relevant to Claim No. <sup>13</sup></th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;">X</td> <td style="padding: 2px;">US, A, 4411027 (H. ALEXANDER et al.) 25 October 1983, see column 3, lines 66-68; column 4, lines 1,2</td> <td style="text-align: center; vertical-align: top; padding: 2px;">1,5</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;">Y</td> <td style="text-align: center; vertical-align: top; padding: 2px;">--</td> <td style="text-align: center; vertical-align: top; padding: 2px;">2,3,6,7,10</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;">X</td> <td style="padding: 2px;">EP, A, 0011528 (INSERM) 28 May 1980, see pages 2,3</td> <td style="text-align: center; vertical-align: top; padding: 2px;">1,4</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;">Y</td> <td style="text-align: center; vertical-align: top; padding: 2px;">--</td> <td style="text-align: center; vertical-align: top; padding: 2px;">2,7</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;">Y</td> <td style="padding: 2px;">FR, A, 2350826 (BATTELLE-INSTITUT) 9 December 1977, see page 3, lines 1-11; claims 2,14</td> <td style="text-align: center; vertical-align: top; padding: 2px;">2</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;">Y</td> <td style="padding: 2px;">FR, A, 2387028 (UNION CARBIDE) 10 November 1978, see page 12, lines 17-27; page 21, lines 27-32</td> <td style="text-align: center; vertical-align: top; padding: 2px;">2,6</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;">Y</td> <td style="padding: 2px;">US, A, 3463158 (E.E. SCHMITT et al.) 26 August 1969, see column 2, lines 24-40; claim 1</td> <td style="text-align: center; vertical-align: top; padding: 2px;">7</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;">Y</td> <td style="padding: 2px;">FR, A, 2364644 (INSERM) 20 September 1976, see page 6</td> <td style="text-align: center; vertical-align: top; padding: 2px;">7</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 2px;"></td> <td style="text-align: center; vertical-align: top; padding: 2px;">--</td> <td style="text-align: center; vertical-align: top; padding: 2px;"></td> </tr> </tbody> </table>			Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>	X	US, A, 4411027 (H. ALEXANDER et al.) 25 October 1983, see column 3, lines 66-68; column 4, lines 1,2	1,5	Y	--	2,3,6,7,10	X	EP, A, 0011528 (INSERM) 28 May 1980, see pages 2,3	1,4	Y	--	2,7	Y	FR, A, 2350826 (BATTELLE-INSTITUT) 9 December 1977, see page 3, lines 1-11; claims 2,14	2	Y	FR, A, 2387028 (UNION CARBIDE) 10 November 1978, see page 12, lines 17-27; page 21, lines 27-32	2,6	Y	US, A, 3463158 (E.E. SCHMITT et al.) 26 August 1969, see column 2, lines 24-40; claim 1	7	Y	FR, A, 2364644 (INSERM) 20 September 1976, see page 6	7		--	
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>																																
<b>IV. CERTIFICATION</b> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; padding: 2px;">           Date of the Actual Completion of the International Search            15th October 1985         </td> <td style="width: 50%; border: none; padding: 2px;">           Date of Mailing of this International Search Report            14 NOV. 1985         </td> </tr> <tr> <td style="border: none; padding: 2px;">           International Searching Authority            EUROPEAN PATENT OFFICE         </td> <td style="border: none; padding: 2px;">           Signature of Authorized Officer  <div style="text-align: right;">             G.L.M. Kruivenberg         </div> </td> </tr> </table>			Date of the Actual Completion of the International Search 15th October 1985	Date of Mailing of this International Search Report 14 NOV. 1985	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer <div style="text-align: right;">             G.L.M. Kruivenberg         </div>																										
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International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer <div style="text-align: right;">             G.L.M. Kruivenberg         </div>																															

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
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# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO.

PCT/NL 85/00027 (SA 10115)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/11/85

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4411027	25/10/83	US-A- 4329743	18/05/82
		CA-A- 1158806	20/12/83
		US-A- 4512038	23/04/85
EP-A- 0011528	28/05/80	FR-A, B 2439003	16/05/80
		US-A- 4279249	21/07/81
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